OSMM&N File No. 4625-016-55X CIP By JPL/ADF/cis

Serial No. 08/131,625

In the Matter of the Application of Prem Paul et al

For **VACCINES RAISING AN IMMUNOLOGICAL RESPONSE AGAINST VIRUSES CAUSING PORCINE RESPIRATORY AND REPRODUCTIVE DISEASES, METHODS OF PROTECTING A PIG AGAINST A DISEASE CAUSED BY A RESPIRATORY AND REPRODUCTIVE VIRUS, A METHOD OF PRODUCING A VACCINE WHICH RAISES AN IMMUNOLOGICAL RESPONSE AGAINST A VIRUS CAUSING A PORCINE RESPIRATORY AND REPRODUCTIVE DISEASE, AND DNA OBTAINED FROM A VIRUS CAUSING A PORCINE RESPIRATORY AND REPRODUCTIVE DISEASE**

The following has been received in the U.S. Patent Office on the date stamped hereon:

[ ] _____ pps. Specification & _____ Claims/Drawings _____ Sheets

[ ] Combined Declaration, Petition & Power of Attorney (___ pages)

[ ] List of Inventor Names and Addresses

[ ] Rule 60 Application [ ] Rule 62 Application

[ ] Notice of Priority [ ] Priority Doc. ( )

[ ] Check for $_____ [X] Dep. Acct. Order Form

[ ] Assignment _____ pages/PTO-1595

[ ] Letter to Official Draftsman

[ ] Letter Requesting Approval of Drawing Changes

[ ] Drawings ____ sheets

[X] Transmittal Letter

[X] Amendment

[X] Information Disclosure Statement [X] PTO-1449

[X] Cited References (4)

[X] Letters from the American Type Culture Collection regarding deposits of microorganisms (3)

[ ] Statement of Relevancy

[ ] IDS/Related/List of Related Cases

[ ] Restriction Response [ ] Election Response

[X] Rule 132 Declarations (1 executed, 1 executed fax copy, 1 unexecuted)

[X] Petition for Extension of Time (2 months)

[ ] Notice of Appeal

[ ] Appeal Brief (in triplicate)

[ ]

Date Mailed: August 17, 1995

IN RE APPLICATION OF: PREM PAUL ET AL

DOCKET NO. 4625-016-55X CIP

SERIAL NO.: 08/131,625

FILED: OCTOBER 5, 1993

FOR: VACCINES RAISING AN IMMUNOLOGICAL RESPONSE AGAINST VIRUSES CAUSING PORCINE RESPIRATORY AND REPRODUCTIVE DISEASES, METHODS OF PROTECTING A PIG AGAINST...

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

Sir:

Transmitted herewith is an amendment in the above-identified application.

☐ No additional fee is required.

☐ Small entity status of this application under 37 C.F.R. §1.9 and §1.27 has been established by a verified statement previously submitted.

☐ Small entity status of this application under 37 C.F.R. §1.9 and §1.27 has been established by a verified statement submitted herewith.

☒ Additional documents filed herewith: Petition for Extension of Time; Rule 132 Declarations (1 executed, 1 executed facsimile copy, 1 unexecuted); Letters from the American Type Culture Collection regarding deposits of microorganisms (3); Information Disclosure Statment; Form PTO-1449; Cited References (4)

The Fee has been calculated as shown below.

	CLAIMS REMAINING AFTER		HIGHEST NUMBER PREVIOUSLY PAID FOR	NO. EXTRA CLAIMS	RATE	CALCULATIONS
TOTAL	34	MINUS	25	= 9	X $ 22 =	$ 198.00
INDEP	3	MINUS	5	= 0	X $ 76 =	$ 0.00
	MULTIPLE DEPENDENT CLAIMS				+ $240 =	$ 0.00
			TOTAL OF ABOVE CALCULATIONS =			$ 198.00
	Reduction by 50% for filing by Small Entity					$ 0.00
	Recordation of Assignment				+ $ 40 =	$ 0.00
			TOTAL			$ 198.00

___ A check in the amount of $_____ is attached.

XX Please charge any additional Fees for the papers being filed herewith and for which no check is enclosed herewith, or credit any overpayment to deposit Account No. 15-0047. A duplicate copy of this sheet is enclosed.

XX If these papers are not considered timely filed by the Patent and Trademark Office, then a petition is hereby made under 37 C.F.R. §1.136, and any additional fees required under 37 C.F.R. §1.136 for any necessary extension of time may be charged to Deposit Account No. 15-0047. A duplicate copy of this sheet is enclosed.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on August 17, 1995.

Signature Date

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C.

Jean-Paul Lavalleye, Ph.D.
Attorney of Record
Registration No. 31,451

Andrew D. Fortney, Ph.D.
Registration No. 34,600

Fourth Floor
1755 Jefferson Davis Highway
Arlington, Virginia 22202
(408) 436-2070
Fax: (408) 436-2075

DOCKET NO. 4625-016-55X CIP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: :

PREM PAUL ET AL : GROUP ART UNIT: 1813

SERIAL NUMBER: 08/131,625 : EXAMINER: CAPUTA

FILED: OCTOBER 5, 1993 :

FOR: VACCINES RAISING AN IMMUNOLOGICAL RESPONSE AGAINST VIRUSES CAUSING PORCINE RESPIRATORY AND REPRODUCTIVE DISEASES, METHODS OF PROTECTING A PIG AGAINST A DISEASE CAUSED BY A RESPIRATORY AND REPRODUCTIVE VIRUS, A METHOD OF PRODUCING A VACCINE WHICH RAISES AN IMMUNOLOGICAL RESPONSE AGAINST A VIRUS CAUSING A PORCINE RESPIRATORY AND REPRODUCTIVE DISEASE, AND DNA OBTAINED FROM A VIRUS CAUSING A PORCINE RESPIRATORY AND REPRODUCTIVE DISEASE

PETITION FOR EXTENSION OF TIME
UNDER 37 C.F.R. 1.136

Assistant Commissioner for Patents
Washington, D.C. 20231

SIR:

It is hereby requested that a two-month extension of time for filing a response to the Official Action dated March 17, 1995 be granted to August 17, 1995.

The required fee of $370.00 is enclosed herewith by check and any further charges may be made against the Attorney of Record's Deposit Account No. 15-0047. A duplicate copy of this sheet is enclosed.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on August 17, 1995.

Signature Date

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C.

Jean-Paul Lavalleye, Ph.D.
Attorney of Record
Registration No. 31,451

Andrew D. Fortney, Ph.D.
Registration No. 34,600

Fourth Floor
1755 Jefferson Davis Highway
Arlington, Virginia 22202
(408) 436-2070
Fax No. (408) 436-2075

4625-016-55X CIP

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF: :

PREM PAUL ET AL : GROUP ART UNIT: 1813

SERIAL NO: 08/131,625 :

FILED: OCTOBER 5, 1993 : EXAMINER: CAPUTA

FOR: VACCINES RAISING AN IMMUNOLOGICAL RESPONSE AGAINST VIRUSES CAUSING PORCINE RESPIRATORY AND REPRODUCTIVE DISEASES, METHODS OF PROTECTING A PIG AGAINST A DISEASE CAUSED BY A RESPIRATORY AND REPRODUCTIVE VIRUS, A METHOD OF PRODUCING A VACCINE WHICH RAISES AN IMMUNOLOGICAL RESPONSE AGAINST A VIRUS CAUSING A PORCINE RESPIRATORY AND REPRODUCTIVE DISEASE, AND DNA OBTAINED FROM A VIRUS CAUSING A PORCINE RESPIRATORY AND REPRODUCTIVE DISEASE

AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Responsive to the Official Action dated March 17, 1995, reconsideration of the above-identified application is respectfully requested in view of the following Amendments and Remarks.

IN THE SPECIFICATION

Page 6, line 2, change "I" to --1--.

Page 16, lines 17 and 20, change "I" to --1--.

Page 13, line 10, change "HI-FIVE™" to --HI-FIVE--;

lines 11, 14, 17 and 23, after "cells", insert --(*Trichoplusian* egg cells)--.

Page 33, line 2, change "_____" to --VR 2428--;

line 3, change "_____, _____ and _____" to --VR 2429, VR 2430, VR 2431 and VR 2474, on October 29, 1992, October 29, 1992, September 29, 1993, September 29, 1993, September 29, 1993, September 29, 1993 and August 31, 1994, respectively--.

Page 41, line 1, change "I" to --1--.

Page 53, lines 7 and 15, change "Tergitol-7" to --TERGITOL-7--.

Page 62, line 11, change "II" to --2--.

Page 63, line 1, change "II" to --2--.

Page 80, line 18, change "POSIBLOT™" to --POSIBLOT--.

Page 85, line 23, change "III" to --3--.

Page 87, line 1, change "III" to --3--.

Page 89, lines 3 and 13, after "cells", insert --(*Trichoplusian* egg cells)--;

lines 4 and 8, change "Excell" to --EXCELL--.

Page 90, line 7, delete ", shown in Figure 25,";

line 13, change "26-29" to --25-27--;

line 17, delete "Figure 26 shows"; and after "cells", insert --(*Trichoplusian* egg cells)--;

line 19, change "(Baculo.PRRSV.6), which" to --(Baculo.PRRSV.6)--;

line 20, change "27" to --25--; and after "cells", insert --(*Trichoplusian* egg cells)--;

line 25, change "28 and 29" to --26 and 27--; and after "cells", insert --(*Trichoplusian* egg cells)--.

Page 91, line 23, change "30" to --28--; and change "31" to --29--;

Page 94, line 12, change "ISU-55 and ISU-3927" to --ISU-55, ISU-3927 and ISU-79--;

line 16, change "_____, _____, _____ and" to --VR 2428, VR 2429, VR 2430, VR 2431 and--;

line 17, change "_____" to --VR 2474--, and after "respectively", insert --, on October 29, 1992, October 29, 1992, September 29, 1993, September 29, 1993, September 29, 1993, September 29, 1993 and August 31, 1994--.

Page 108, lines 9 and 11, change "32" to --30--;

lines 10, 12 and 20, change "33" to --31--.

Page 109, line 1, change "VIII" to --IX--;

line 14, change "34" to --32--.

IN THE CLAIMS

Please cancel Claims 1-9 and 14-30 without prejudice.

Please amend Claim 10 as follows:

--10. (Amended) A method of protecting a pig from [infection against a virus which causes] a porcine reproductive and respiratory disease, comprising administering an effective amount of the vaccine of Claim [1] 35 to a pig in need of protection against [infection by] said [virus] disease.--

Please add the following new claims:

--31. A biologically pure virus which causes porcine reproductive and respiratory syndrome (PRRS), wherein inoculation of five-week-old colostrum-deprived, caesarean-derived pigs with 10^5 $TCID_{50}$ of said virus results in lesions in at least 51.9% of lung tissue 10 days post-infection.

32. The biologically pure virus of Claim 31, selected from the group consisting of ISU-12 (VR 2385 and VR 2386), ISU-22 (VR 2429), ISU-79 (VR 2474) and ISU-28; or a virus exhibiting the identifying characteristics of a virus in said group.

33. The biologically pure virus of Claim 32, selected from the group consisting of ISU-12 (VR 2385 and VR 2386), ISU-22 (VR 2429) and ISU-79 (VR 2474).

34. The biologically pure virus of Claim 31, wherein said virus has less than 90% polynucleotide sequence identity to Lelystad virus in any one of open reading frames 5, 6 or 7.

35. A composition comprising the biologically pure virus of Claim 31 and a physiologically acceptable carrier.

36. A vaccine which protects a pig against porcine reproductive and respiratory syndrome (PRRS), comprising a

live, inactivated or attenuated virus and a physiologically acceptable carrier, wherein prior to inactivation or attenuation, said virus is the virus of Claim 31.

37. The vaccine of Claim 36, wherein said virus is attenuated and is prepared by serial passage in cell culture.

38. The vaccine of Claim 36, which raises an effective immunological response in a pig against a virus which causes PRRS.

39. The vaccine of Claim 36, wherein lung lesions in said five-week-old colostrum-deprived, caesarean-derived pigs are reduced by a statistically significant amount, relative to lung lesions in uninoculated five-week-old colostrum-deprived, caesarean-derived pigs.

40. The vaccine of Claim 36, wherein said effective amount is one which lowers the average clinical respiratory score of a group of colostrum-deprived, caesarean-derived pigs inoculated with said vaccine, then subsequently challenged with live PRRS virus, relative to a group of identically challenged colostrum-deprived, caesarean-derived pigs not inoculated with the vaccine.

41. A composition for protecting a pig from PRRS, comprising the vaccine of Claim 36 and an adjuvant.

42. A biologically pure virus selected from the group consisting of ISU-51 (VR 2429), ISU-55 (VR 2430), ISU-3927 (VR 2431) and ISU-1894; or a virus exhibiting the identifying characteristics of a virus in said group.

43. The biologically pure virus of Claim 42, selected from the group consisting of ISU-51 (VR 2429), ISU-55 (VR 2430), ISU-3927 (VR 2431) and ISU-1894.

44. The biologically pure virus of Claim 42, wherein said virus has less than 90% polynucleotide sequence homology to Lelystad virus in any one of open reading frames 5, 6 or 7.

45. A vaccine which protects a pig against porcine reproductive and respiratory syndrome (PRRS), comprising an effective amount of the biologically pure virus of Claim 43 and a physiologically acceptable carrier.

46. The vaccine of Claim 45, wherein said virus is live, inactivated or attenuated.

47. The vaccine of Claim 46, wherein said virus is attenuated and is prepared by serial passage in cell culture.

48. The vaccine of Claim 45, which raises an effective immunological response in a pig against a virus which causes PRRS.

49. The vaccine of Claim 45, wherein lung lesions in colostrum-deprived, caesarean-derived pigs inoculated with said vaccine, then challenged with live porcine reproductive and respiratory syndrome virus, are reduced by a statistically significant amount, relative to lung lesions in uninoculated colostrum-deprived, caesarean-derived pigs.

50. The vaccine of Claim 45, wherein said effective amount is one which lowers the average clinical respiratory score of a group of colostrum-deprived, caesarean-derived pigs inoculated with said vaccine, then subsequently challenged with live PRRS virus, relative to a group of identically challenged colostrum-deprived, caesarean-derived pigs not inoculated with the vaccine.

51. A composition for protecting a pig from PRRS, comprising the vaccine of Claim 45 and an adjuvant.

52. A method of protecting a pig from a porcine reproductive and respiratory disease, comprising administering an effective amount of the vaccine of Claim 45 to a pig in need thereof.

53. The method of Claim 52, wherein said vaccine is administered orally or parenterally.

54. The method of Claim 53, wherein said vaccine is administered intramuscularly, intradermally, intravenously, intraperitoneally, subcutaneously or intranasally.

55. The method of Claim 54, wherein said vaccine is administered to a sow in need of protection against infection by said virus.

56. A biologically pure virus which causes porcine reproductive and respiratory syndrome virus and has a nested set of mRNAs, wherein said virus has either (a) 7 or more subgenomic mRNAs or (b) from 1 to 4 deletions in its mRNAs, relative to ISU-1894.

57. The virus of Claim 56, having from 1 to 4 deletions in its mRNAs, relative to ISU-1894.

58. A vaccine which protects a pig against porcine reproductive and respiratory syndrome (PRRS), comprising an effective amount of the biologically pure virus of Claim 56 and a physiologically acceptable carrier.

59. A method of protecting a pig from a porcine reproductive and respiratory disease, comprising administering an effective amount of the vaccine of Claim 58 to a pig in need thereof.

60. The biologically pure virus of Claim 42, selected from the group consisting of ISU-51 (VR 2429) and ISU-3927 (VR 2431); or a virus exhibiting the identifying characteristics of a virus in said group.--

SUPPORT FOR AMENDMENTS

Support for the amendment to page 13, lines 11, 14, 17 and 23, can be found in the specification on page 13, lines 9-10.

Support for Claim 31 can be found in the specification on page 32, lines 6-8 and 18-24, page 95, lines 1-3, page 96, lines 12-16, page 97, first 4 rows of data in Table 6, page 103, lines 7-11, page 104, rows 2-4 of data in Table 14 (lines 4-6 as marked) and page 107, last three rows of data in Table 16. Support for Claims 32, 33, 42, 43 and 60 can be found in the support for Claims 31 and on page 32, lines 22-26, page 33, lines 1-3 and page 94, lines 11-17 of the specification. Support for Claims 34 and 44 can be found on page 30, lines 4-10, page 85, lines 23-24, and page 86, lines 1 and 4-5. Support for Claim 35 can be found in the support for Claim 31 and in Claim 1 as originally filed. Support for Claims 36,

45, 46 and 58 can be found on page 21, lines 24-26, page 22, lines 1-16, page 25, lines 20-26, page 26, lines 1-10 and page 27, lines 1-6. Support for Claims 37 and 47 can be found on page 27, lines 1-4. Support for Claims 38 and 48 can be found in Claim 1 as originally filed and in the specification on page 5, lines 15-24. Support for Claims 39 and 49 can be found in the support for Claims 31 and 36, and also on page 33, lines 20-23 and page 103, lines 13-17. Support for Claims 40 and 50 can be found in the support for Claims 31, 36 and 39, and on page 101, lines 19-24, page 102, lines 1-2 and Table 13, page 109, lines 1-21, and Figure 32 (Fig. 34 as originally filed). Support for Claims 41 and 51 can be found on page 34, lines 6-15. Support for Claims 52 and 59 can be found on page 34, lines 24-26 and page 35, lines 1-4. Support for Claim 53 can be found on page 36, lines 18-19. Support for Claim 54 can be found on page 36, lines 20-22. Support for Claim 55 can be found in Claim 13 as originally filed. Support for Claims 56 and 57 can be found on page 33, lines 4-7, page 94, Table 5 and lines 18-22, and page 108, lines 7-20 and Figures 30-31 (Figs. 32-33. Therefore, no new matter is introduced by the above amendments.

Claims 1-9 and 14-30 have been canceled. Claims 31-60 have been added. Thus, Claims 10-13 and 31-60 are active in the present application.

REMARKS

Applicants thank Examiner Caputa for the helpful and courteous discussion held with their representative on June 1, 1995. As discussed, Applicants have amended the claims to include:

(A) a biologically pure "high virulence" virus, in which a specific amount of the virus results in lesions in at least 51.9% of lung tissue in a model piglet 10 days post-infection (see Claims 31-34);

(B) a biologically pure non-"high virulence" virus, corresponding to a deposited strain VR 2429, VR 2430, VR 2431 or ISU-1894, or a virus having the identifying characteristics of such a strain (see Claims 42-44 and 60); and

(C) viruses showing one or more surprising and unexpected characteristics (see Claims 56-57).

Also as discussed, the claims also include compositions comprising such viruses (Claims 35, 41 and 51), vaccines comprising such viruses, which may be in live, inactivated or attenuated form (Claims 36-40, 45-50, and 58), and methods of protecting a pig from a porcine reproductive and respiratory disease using the same (Claims 10-13, 52-55 and 59). Furthermore, evidence is submitted herewith which:

(A) distinguishes the presently claimed PRRS viruses, compositions and vaccines from [1] the virus which causes PNP (see the fax coy of Declaration from Dr.

Prem Paul, attached hereto), [2] VR 2332 and [3] Lelystad virus (see "Declaration No. 2" of Dr. Paul attached hereto; the executed copy of which will be filed as soon as possible), and

(B) further supports the *in vivo* utility of the present vaccine and method (see the executed Declaration of Dr. Melissa Lum, attached hereto).

The following remarks shall summarize and expand upon other topics discussed.

The present invention concerns a virus, composition, vaccine and method of protecting pigs against PRRS. In recent years, North American and European swine herds have been susceptible to infection by new strains of respiratory and reproductive viruses (see page 1 of the specification). One such disease is now known as PRRS (porcine respiratory and reproductive syndrome).

The symptoms of PRRS (as it originally appeared) include a reluctance to eat (anorexia), a mild fever (pyrexia), cyanosis of the extremities (notably bluish ears), stillbirths, abortion, high mortality in affected litters, weak-born piglets and premature farrowing. The majority of piglets born alive to affected sows die within 48 hours (see page 2, last 5 lines and page 3, line 1 of the specification).

Recently, a more virulent form of PRRS has been occurring with increased incidence in 3-8 week old pigs in the midwestern United States. Typically, healthy 3-5 week old

pigs are weaned and become sick 5-7 days later (see page 5, lines 7-10 of the specification).

The pig farming industry has been and will continue to be adversely affected by these porcine reproductive and respiratory diseases and new variants thereof, as they appear (see page 6 of the specification, last paragraph). Economic losses from PRRS occur from loss of pigs from abortions, stillborn pigs, repeat breeding, pre-weaning and postweaning mortality, reduced feed conversion efficiency, increased drug and labor cost and have been estimated to cost approximately $236 per sow in addition to loss of profits (see Polson et al., Financial implications of mystery swine disease (MSD), *Proc. Mystery Swine Disease Committee Meeting*, Denver, Co., 1990, pp. 8-28). This represents a loss of $23,600 for a 100 sow herd or $236,000 for a 1000 sow herd. Understandably, there is both an economic incentive and a substantial public health benefit to be derived from protecting farm animals from PRRS.

The present invention represents a significant advance in the development of effective PRRS protection. In addition to the evidence in Experiments IV (pages 101-103) and IX (page 109 and original Figure 34) the present virus, composition, vaccine and method are effective in protecting a pig against subsequent challenge with live PRRS virus.

By the definition of "effective" in the specification (see page 33, lines 16-23), the results in Table 13 on page

102 of the specification demonstrate that each of the biologically pure viruses tested is effective in reducing the severity of at least one symptom of PRRS. Two of the tested viruses were effective in reducing the severity of all respiratory symptoms monitored, and one isolate exhibited commercial promise for use as a live vaccine (note particularly page 103, lines 4-5 of the specification).

Figure 32 (corresponding to originally-filed Fig. 34, a copy of which is attached hereto) graphically demonstrates the effectiveness of a representative example of the present vaccine containing a "high-virulence" isolate (plaque-purified ISU-12 [VR 2385]). When administered either intranasally or intramuscularly, this vaccine significantly reduced the average gross lung lesion scores to about 30% of the scores of the control group. Thus, the efficacy of this exemplary PRRS vaccine is proven (see page 109, lines 19-21 of the specification).

Furthermore, in subsequent studies, a cross-protection study was performed in four-week-old, PRRSV-seronegative commercial pigs (see the Declaration of Dr. Melissa Lum, attached hereto). The test pigs were vaccinated intramuscularly with $10^{5.8}$, $10^{5.3}$, $10^{5.5}$ and $10^{5.7}$ $TCID_{50}$ of PRRSV isolates ISU-12 p26, ISU-51 p15, ISU-55 p15 and ISU-3927 p16, respectively (the term "p##" refers to the number of virus passages in the CRL11171 cell line). Age-matched PRRSV-seronegative pigs served as non-vaccinated controls.

Five weeks later, the pigs were challenged intranasally with $10^{4.6}$ $TCID_{50}$ of ISU-12 p6. Lung lesions were examined 10 days after the ISU-12 p6 challenge. The results are presented in Table 1 on page 2 of the Declaration of Dr. Lum, reproduced below for convenience:

TABLE 1

Vaccinate Group	Gross Lung Lesion Score[a]
Control	47.2
ISU-12 p26	7.2
ISU-51 p15	8.1
ISU-55 p15	16.6
ISU-3927 p16	20.9

[a]: Gross lung lesion scores represent the percent of lung affected (i.e., the percent of lesions in the lung). The score is based on a scale of from 0 to 100 percent of lung affected.

All vaccinate groups (i.e., those intramuscularly vaccinated with an ISU isolate) demonstrated significantly lower ($p < 0.01$) gross lung lesion scores than non-vaccinated controls. Thus, the data in Table 1 above demonstrate that ISU-12 (attenuated by 26 passages in cell culture), ISU-51, ISU-55 and ISU-3927 provide protection for pigs against disease caused by ISU-12, one of the most virulent strains of PRRSV virus known (see paragraph 5, page 3 of said Declaration).

Therefore, the present virus, composition, vaccine and method are effective in protecting pigs against highly virulent forms of PRRSV. To date, no one has demonstrated efficacy of any other virus or vaccine in protecting against highly virulent forms of PRRSV.

The present inventors were the first to isolate, identify and characterize such highly virulent forms of PRRSV. Consequently, they are also the first to develop exemplary vaccines to protect against such highly virulent PRRS viruses. The knowledge provided by the present invention will greatly expand our understanding of the disease and its corresponding viruses, and will help lead to a comprehensive commercial vaccine (e.g., to be truly comprehensive, a vaccine must be effective against challenge by highly virulent strains of the virus).

Finally, the variations between the presently claimed viruses and prior viruses could not have been predicted based on the knowledge in the field prior to the present invention. Therefore, the present invention is fully patentable.

The objection to the specification and rejection of Claims 1-13 under 35 U.S.C. 112, 1st paragraph, are respectfully traversed. As discussed above, the data in the specification and in the accompanying Declaration of Dr. Lum clearly provides sufficient evidence to establish the effectiveness *in vivo* in pigs of the present invention. Furthermore, the specification provides sufficient guidance to

one of ordinary skill to enable one to make and use the present vaccine (see from page 18, line 18 through page 28, line 22, page 31, lines 6-24, page 32, line 6 through page 35, line 12, page 36, line 8 through page 41, line 2, Experiment VI on page 101-103 and Experiment IX, page 109). Consequently, no undue burden of experimentation is born by those of ordinary skill in the art with regard to how to make and use the present vaccine.

Therefore, this ground of objection and rejection is unsustainable, and should be withdrawn.

The rejection of Claims 6-8 under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Christianson et al is respectfully traversed.

Christianson et al disclose the SIRS virus isolate VR-2332. In one experiment, Christianson et al inoculate sows three weeks prior to farrowing with lung homogenate from an infected field pig (page 486, right-hand column, lines 7-10 and second full paragraph, lines 1-4). In another experiment, the third passage of the virus (VR 2332) in CL2621 cells is used as the inoculum.

Christianson et al examined the brain, heart, lung, liver, spleen, kidney and ileum from fetuses, pigs and sows (page 486, left-hand column, lines 9-10 from the bottom [next-to-last paragraph] and right-hand column, first full paragraph, last 5 lines). However, microscopic lesions were not seen in tissues from pigs or fetuses in inoculated litters

(page 487, right-hand column, lines 1-2 of the first full paragraph, and page 488, left-hand column, lines 2-6 of the last full paragraph).

Christianson et al also refer to another report which discloses replication of the respiratory component of the disease in gnotobiotic pigs (see Collins et al, *J. Vet. Diagn. Invest.*, 4:117 (1992); submitted with the Information Disclosure Statement filed on June 3, 1994). Collins et al report that lungs of infected gnotobiotic piglets did not have gross lesions, and that gross lesions were absent in infected sows (see page 119, left-hand column, line 5 below the subtitle "Results", and right-hand column, line 1 of the first full paragraph).

In contrast to these results, conventional pigs infected by a representative example of the present "high virulence" virus (ISU-12) showed visible lung lesions seven days post-infection (DPI) involving from 20% to 40% of the lung (see page 54, lines 13-21 and page 55, lines 20-23 of the specification). Further, pigs infected with naturally-occurring pneumonia exhibited lung lesions characterized by proliferative bronchiolitis and alveolitis (page 48, lines 20-22). Lung tissue samples from 5 other acutely affected 5-6 week old pigs exhibited gross lung lesions typical of a viral pneumonia (page 49, lines 6-8). Thus, naturally-occurring lesions produced by the present "high virulent" virus were not observed by either Christianson et al or Collins et al,

regardless of the conditions or type of pigs which they inoculated.

In addition, colostrum-deprived caesarean-derived (CDCD one-day-old gnotobiotic pigs inoculated with ISU-12 (representative of the present so-called "high virulence" viruses) showed both macroscopic and microscopic lesions in the lung by 5 DPI (see page 57, lines 9-17 of the specification). These lesions persisted up to 35 DPI (see page 58, lines 14-15). Heart lesions were also observed (see page 59, lines 14-18). Thus, the disease caused by the viruses of the present Claims 31 is a different type (gross lung and heart lesions verses no lesions) of disease, rather than a different kind, than the disease caused by the virus of Christianson et al and Collins et al (also see page 60, lines 15-17 of the specification).

Christianson et al neither disclose nor suggest a virus having the virulence or effects of the viruses claimed in the present Claim 31. Consequently, Christianson et al neither anticipate nor suggest a virus in which inoculation of five-week-old colostrum-deprived, caesarean-derived pigs with a 10^5 $TCID_{50}$ dosage results in lesions in at least 51.9% of lung tissue 10 days post-infection (i.e., Claim 31 and claims dependent therefrom). Thus, the "high-virulence" viruses of the present Claim 31 are fully patentable over Christianson et al.

With regard to the present Claim 42 above (a biologically pure virus selected from the group consisting of ISU-51, ISU-55, ISU-3927 and ISU-1894, or a virus exhibiting the identifying characteristics of a virus in this group), Christianson et al neither disclose nor suggest that other biologically pure viruses can be obtained. Furthermore, the published patent references concerning VR 2332 also fail to disclose or suggest the possibility of other biologically pure viruses being isolated (see Collins et al, International Patent Publication No. WO 93/06211 ["WO '211"]; Chladek et al, Canadian Patent Publication No. 2,076,744; and Collins et al, International Patent Publication No. WO 93/03760 ["WO '760"]; each of which was submitted with the Information Disclosure Statement filed on June 3, 1994). Thus, Christianson et al neither anticipate nor suggest the specific biologically pure viruses of Claim 42.

Christianson et al neither disclose nor suggest a biologically pure virus exhibiting the identifying characteristics of ISU-51, ISU-55, ISU-3927 or ISU-1894. For example, in a study performed by the present Inventors on 5-week-old CDCD piglets, ISU-3927 did not cause encephalitis at all, and did not produce symptoms of myocarditis until 21 DPI (see the experimental description on page 95, lines 1-8, and the results in Tables 7-12 on pages 98-100 of the specification).

By contrast, the virus disclosed by Christianson et al, VR 2332, produces some level of encephalitis (2 out of 6 piglets) and myocarditis (1 out of 6 piglets) in three-day-old gnotobiotic piglets at 8 DPI (see page 30, lines 1-8 and page 31, lines 18-26 of WO '211). Thus, VR 2332 does not have the identifying characteristics of ISU 3927.

Five-week-old CDCD piglets are more susceptible to and more severely affected by infection by PRRS virus than are three-day-old gnotobiotic piglets (compare the results on pages 57-58 of the specification in the one-day-old gnotobiotic pig study [using ISU-12] with the results in the CDCD piglet study on pages 95-101 [also using ISU-12]). Christianson et al neither disclose nor suggest that another biologically pure virus can be isolated which is less virulent, yet still protective against subsequent challenge with a highly virulent strain of PRRSV. Thus, ISU-3927 and viruses having the identifying characteristics thereof are fully patentable over Christianson et al.

Similarly, 5-week-old CDCD piglets inoculated with ISU-51 show a very low mean clinical respiratory score at 5 and 10 DPI (i.e., the piglets showed little, if any, respiratory distress; see p. 35, lines 13-29, p. 36, lines 1-8, p. 105, lines 15-19 and the results in Table 16 on p. 107). At 10 DPI, only one piglet out of twelve inoculated with ISU-51 showed rhinitis and only two out of the twelve piglets showed encephalitis or myocarditis.

By contrast, piglets infected with VR 2332 are much more likely to exhibit rhinitis (four out of six gnotobiotic pigs), encephalitis (2/6) and myocarditis (1/6) than piglets inoculated with ISU-51. Thus, since the same or higher percentage of less-susceptible gnotobiotic pigs of Christianson et al showed these symptoms than did the more susceptible, more severely affected 5-week-old CDCD pigs tested by the present Inventors, the types and severity of clinical pathological conditions caused by the virus of Christianson et al are more severe than those caused by ISU-51.

Furthermore, as demonstrated by the results in the accompanying Declaration of Dr. Lum, ISU-51 (passaged 15 times) provided protection against highly virulent PRRS. Thus, similar to ISU-3927, Christianson et al fail to suggest that less virulent strains of PRRS virus which also provide protection against highly virulent PRRS can or will be found. Thus, ISU-51 and viruses having the identifying characteristics of ISU-51 are fully patentable over Christianson et al.

ISU-55 and ISU-1894 can be distinguished from VR 2332 by their genetic and protein sequence information. Data comparing sequence identities of open reading frames (ORFs) 2-7 of ISU-55, ISU-3927 and VR 2332 can be found in the Table on page 5 of the accompanying Declaration No. 2 of Prof. Prem Paul. The Table is reproduced herein below for convenience

(data on the Lelystad virus, disclosed by Wensvoort et al [also cited against the present invention], is also included):

Table: Nucleotide and deduced amino acid sequence identities (%) of ORFs 2 to 5 of PRRSV

ORF 2	ISU55	ISU1894	VR2332	LV
ISU55	**	95	97	61
ISU1894	96	**	96	57
VR2332	97	97	**	59
LV	66	66	66	**
ORF 3				
ISU55	**	93	94	56
ISU1894	93	**	96	55
VR2332	94	97	**	56
LV	62	63	63	**
ORF 4				
ISU55	**	96	95	67
ISU1894	94	**	98	66
VR2332	95	98	**	65
LV	63	66	65	**
ORF 5				
ISU55	**	89	89	51
ISU1894	90	**	96	53
VR2332	91	97	**	53
LV	63	62	63	**

Note: The amino acid sequence comparisons are presented in the upper right half, and the nucleotide sequence comparisons are presented in the lower left half.

Accordingly, Christianson et al do not anticipate the present Claims 42-55.

Three hypervariable regions have been identified in ORF 5 of PRRSV by comparing the amino acid sequences of PRRSV isolates. Amino acid variations in these three regions are significant, and are not structurally conserved. For example, the amino acid sequence identity between VR 2332 and ISU 55 is 91% in ORF 5, and between VR 2332 and ISU 1894, 97%. Computer analysis indicates that all three hypervariable regions are hydrophilic and antigenic. Thus, it is likely that these regions are exposed to the viral membrane and are under host immune selection pressure.

The present ISU-55 (as the 15th passage in CRL11171 cells) is also effective in protecting pigs against highly virulent PRRS (see the Declaration of Dr. Lum). Christianson et al neither disclose nor suggest that a virus having nucleic acids and proteins as different as ISU-55 has, relative to VR 2332, will also be effective in protecting pigs against highly virulent PRRS. Thus, ISU-55 and viruses having the identifying characteristics thereof are fully patentable over Christianson et al.

Finally, Christianson et al do not suggest that a virus as different from VR 2332 as is ISU-1894 can or will be discovered. Thus, ISU-1894 and viruses having the identifying characteristics thereof are fully patentable over Christianson et al.

The pathogenicity studies in caesarean-derived colostrum-deprived (CDCD) pigs described the present application show

that VR 2385, VR 2429 and ISU-79 are highly pathogenic, whereas ISU-55, ISU-1894 and VR 2431 are not as pathogenic. For example, VR 2385, VR 2429 and ISU-79 produced from 50 to 80% consolidation of the lung tissues in experimentally-infected five-week-old CDCD pigs necropsied at 10 days post inoculation, whereas VR 2430, ISU-1894 and VR 2431 produced only 10 to 25% consolidation of lung tissues in the same experiment (see the paragraph bridging pages 9-10 in Declaration No. 2 of Prof. Paul).

Thus, highly virulent strains of PRRSV (i.e., those viruses causing at least 50% consolidation of lung tissues in the test pigs recited in Claim 31) are less similar to and possess fewer identifying characteristics of VR 2332 (such as pathology in the standard test animals) than the less virulent strains ISU-51, ISU-55, ISU-1894 and ISU-3927 described in the above-identified application, based on the published pathology of VR 2332. Therefore, both the present "high virulence" and less virulent viruses recited in Claims 31 and 42 are fully patentable over Christianson et al.

Finally, the genomic sequence of VR 2332 has been determined (see, for example, Murtaugh et al, *Proc. Allen D. Leman Swine Conference*, Minneapolis, MN, pp. 43-45 (1993), and U.S. application Serial Nos. 08/301,435 and 08/478,316). No report of an unusual number of subgenomic mRNAs or mRNA deletions have been reported. If such unusual characteristics of the mRNAs of the VR 2332 existed, they would have been reported. Thus, Christianson et al do not inherently disclose or suggest a biologically pure virus which has either (a) 7 or

more subgenomic mRNAs or (b) from 1 to 4 deletions in its mRNAs, relative to ISU-1894 (ISU-1894 exhibits mRNAs typical of PRRS viruses in their number and length). Therefore, the viruses of the present Claim 56 are fully patentable over Christianson et al.

Consequently, this ground of rejection is unsustainable and should be withdrawn.

The rejection of Claims 6 and 7 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Dea et al or Morin et al is respectfully traversed.

Dea et al disclose an antigenic variant of swine influenza virus causing proliferate and necrotizing pneumonia in pigs. Morin et al also disclose severe proliferative and necrotizing pneumonia in pigs, a newly recognized disease.

Proliferative and Necrotizing Pneumonia (PNP), now known as atypical Swine Influenza (aSI), and porcine reproductive and respiratory syndrome (PRRS) are different diseases caused by viruses which belong to different virus families. For example, PNP is a disease caused by swine influenza virus (SIV), whereas PRRS is a disease caused by PRRS virus (PRRSV). The comparative pathologies of the diseases differ as shown in the table below (see paragraph 4, page 2 of the accompanying fax Declaration of Prof. Paul):

TABLE

Swine Viral Pneumonia Comparative Pathology

Lesion	PRRS(p)	PRRS(o)	SIV	PNP	Iowa
Type II	+	+++	+	+++	++++
Inter. thickening	++++	+	+	+	+
Alveolar exudate	+	+++	++	++	+++
Airway necrosis	-	-	++++	++++	-
Syncytia	-	++	+/-	++	+++
Encephalitis	+	+++	-	-	+
Myocarditis	+/-	++	-	-	+++

Thus, swine influenza/PNP is characterized by highly severe airway necrosis, but not by encephalitis or myocarditis. By contrast, PRRS (including the disease(s) caused by the Iowa strain of PRRSV) is characterized by the appearance of encephalitis and myocarditis, but not by airway necrosis (see paragraph 5, page 2 of the fax Declaration of Prof. Paul).

SIV has a negative-sense, multiple-stranded genome (8 strands). Furthermore, SIV hemagglutinates, and cell cultures of SIV are not characterized by a nested set of mRNA's. By contrast, PRRSV does not hemagglutinate, but does contain a positive-sense, single-stranded genome ("positive-sense" means that the genome codes directly for protein(s)). Further, cell cultures of PRRSV are characterized by a nested set of mRNA's (see the above-identified application, particularly page 83). Even further, pigs suffering from the disease caused by the Iowa strain of PRRSV are seronegative for influenza, including the virus(es) associated with PNP (see page 18, lines 14-18 of

the above-identified application and paragraphs 6-7, page 3 of the accompanying fax Declaration of Prof. Paul).

The molecular sizes of the proteins encoded by the genomes of each of these viruses are different, and there is no antigenic cross-reactivity between SIV (the virus which causes PNP) and PRRSV (see paragraph 8, page 3 of the accompanying fax Declaration of Prof. Paul).

Based on the above differences in the identifying characteristics of these viruses and the diseases which they cause, it is generally accepted in the field of veterinary medicine that SIV (the virus which causes PNP) and PRRSV belong to different virus families (see paragraph 9, page 3 of the accompanying fax Declaration of Prof. Paul).

Consequently, the virus disclosed by Dea et al and Morin et al (aSIV, which causes PNP) neither anticipates nor suggests the present viruses. As a result, the present invention is fully patentable over Dea et al and Morin et al.

The rejection of Claims 6-8 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Wensvoort et al is respectfully traversed.

Wensvoort et al disclose the Lelystad virus. However, as shown by the comparison of genomic and amino acid sequence data in the Table above (taken from the accompanying Declaration No. 2 of Prof. Paul), the presently claimed PRRS viruses and Lelystad virus are quite different. In fact, those of ordinary skill in this field would consider Lelystad virus to be a different genotype from the presently claimed

PRRS viruses (see the last paragraph on page 6 of Declaration No. 2 of Prof. Paul).

Furthermore, as demonstrated by the results in the table of Declaration No. 2 of Prof. Paul (presented above), Lelystad virus is genetically considerably further removed from the present invention than is VR 2332, over which all of the presently claimed viruses, compositions, vaccines and methods are fully patentable.

Therefore, the virus disclosed by Wensvoort et al neither anticipates nor suggest the present invention. Consequently, this ground of rejection is unsustainable, and should be withdrawn.

The rejection of Claims 1-5 and 9-13 under 35 U.S.C. 103 as being unpatentable over Wensvoort et al or Christianson et al in view of Carlson et al is respectfully traversed.

The discussions above regarding the Wensvoort et al and Christianson et al are incorporated herein with regard to this ground of rejection.

Carlson et al disclose an encephalomyocarditis virus vaccine. Carlson et al are silent with regard to PRRS virus. Thus, Carlson et al cannot cure the deficiencies of Wensvoort et al and Christianson et al with regard to the presently claimed viruses (from which the presently claimed vaccine depends).

Therefore, this ground of rejection is also unsustainable and should be withdrawn.

The rejection of Claims 1-13 under 35 U.S.C. 112, second paragraph, is, in part, obviated by appropriate amendment, and is, in part, respectfully traversed.

The phrase "biologically pure" is neither vague nor indefinite. A significant number of U.S. patents in this area have been issued containing claims to "biologically pure" microorganisms, including viruses. Furthermore, the present specification defines "biologically pure" (see page 32, lines 18-22).

In the context of its use in the specification, TERGITOL-7 agar is generically described as a medium for growing bacteria. This generic knowledge regarding TERGITOL-7 agar is confirmed by Christianson et al (cited against the present application).

In addition, the components of the present composition and vaccines are now clearly recited in the above claims. Therefore, this ground of rejection is no longer sustainable and should be withdrawn.

The objection to the specification and the rejection of Claims 4 and 8 under 35 U.S.C. 112, first paragraph, for failure to provide complete deposit information has been obviated by appropriate amendment.

As described on pages 32-33 and 94 of the specification, the claimed viruses have been deposited under the Budapest Treaty at the American Type Culture Collection. All restrictions on access to the deposited viruses will be irrevocably removed upon the grant of a patent from the

present application. The deposits will be replaced should the deposited samples become non-viable.

Furthermore, the specification has been amended to include the full name and address of the depositary and the dates on which the deposits were made. Support for the deposits and for the amendments to the specification can be found on page 32, last two lines, page 33, lines 1-3, and page 94, lines 11-17 of the specification, and in the attached letters dated November 12, 1992, January 10, 1994 and October 28, 1994, from the American Type Culture Collection. Thus, the claimed virus has been made available to the public, and Applicants have otherwise met all of the requirements of 35 U.S.C. 112 for deposits of biological materials.

Applicants note that virus isolate ISU-1894 has been deposited. However, the American Type Culture Collection has not yet assigned an accession number for this deposited strain. Consequently, the specification cannot be amended to reflect complete deposit information for this deposited strain.

Accordingly, this ground of rejection is unsustainable, and should be withdrawn.

On February 18, 1994, a request for approval of corrections to the informal drawings/figures was made. The four sheets of informal Fig. 19 were renumbered in accordance with 37 C.F.R. 1.84(t). Figs. 25-26 were canceled because the corresponding photographs cannot be located. Subsequent informal Figures 27-34 were renumbered. The specification has now been amended to reflect the renumbering of original Figs.

27-34 as new Figs. 25-32. Thus, approval of the corrections to the figures as submitted on February 18, 1994, is respectfully requested.

Accordingly, this application is in condition for allowance. Early notice to that effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Jean-Paul Lavalleye, Ph.D.
Attorney of Record
Registration No. 31,451

Andrew D. Fortney, Ph.D.
Registration No. 34,600

Crystal Square Five - Fourth Floor
1755 South Jefferson Davis Highway
Arlington, VA 22202
(408) 436-2070
Fax: (408) 436-2075
ADF/cjs